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Review Article

The Existence and Signaling of Cancer Stem Cells in Non-Small Cell Lung Cancer

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Abstract

Non-small lung cancer (NSCLC) is one of the most aggressive malignant tumor diseases accounting for a large group of all lung cancer cases, and patients with NSCLC have very poor prognosis with short survival time and high reccurence rates after therapy. This phenomenon could be illustrated by the existence of cancer stem cells (CSCs) which is well supported by a large number of previous studies. Herein we generalize signaling and mechanisms (mainly including WNT, notch and hedgehog pathways) involved in cancer stemness in NSCLC according to recently-published data with briefly-described CSC identification and evaluation methods. All of above will help lead to new advances in therapy against CSCs and improvements in prognosis of NSCLC patients.

Introduction

As one of the most aggressive malignant diseases, lung cancer remains a leading course of cancer death which have posed a serious threat to people's lives in western countries [1-3]. As one type of lung cancer, cases of the non-small cell lung cancer (NSCLC) account for almost 70% of all lung cancer cases [2]. The most common types of NSCLCs include squamous cell carcinoma, adenocarcinoma and large cell carcinoma, and each of them can occur at different histologic grades including well-differentiated, moderately-differentiated and poorly-differentiated cases [4]. To treat patients with NSCLCs at higher histologic grades, chemotherapy and radiotherapy other than surgery were often used. However, compared to small cell carcinoma, NSCLCs especially at poorly differentiated grades often show relative strong resistance towards chemotherapy [5-6]. Thus, there is a clear need to find therapeutic strategies against NSCLC.

To better improve the effect of chemotherapy, many approaches have been used including the inhibition of surviving pathways such as EGFR, AKT, WNT pathways and the sensitization of apoptosis using small molecues [7-9]. After cell exposure in anti-cancer reagents, most cells undergo the process of apoptosis whereas a small portion of tumor cells exhibit considerable tolerance towards these drugs and failed to be eliminated. This phenomenon could be explained by the tumor heterogeneity and the existence of cancer stem cells (CSCs) [10-11].

CSCs, also named as tumor-initiating cells, are one kind of cells which posess higher self-renewal capacity, higher proliferation rate, the increased capacity of tumor invasion, metastasis and tumor formation [12]. The existence of the CSC group in cancer cells confers resistance towards conventional chemotherapy in patients with NSCLC and lead to poor prognosis and higher frequency of tumor reccurence after treatment [13]. In this review we focus on diverse pathways involved in cancer stemness in NSCLC which is helpful to the improvement of the CSC theory and new advances in clinical therapies against NSCLC. Besides, this review also provided a brief description of CSC identification and evaluation methods.

Identificaion of CSC in NSCLC

Sides-Population Cells Represents the Group of CSCs

Although there has been a rapid advance in the field of CSC research in NSCLCs which have provided cause for optimism for the apply of more reliable cancer therapies, the identification of CSCs in NSCLCs still remains a challenge [14]. A small portion of CSC cells can be enriched in the side population cells (SP) after fluorescence activated cell sorting due to ABC transporters such as ABCG2 activation in this group of cells which cannot be stained with Hoechst 33342, compared with those cells treated with the pump inhibitor verapamil [15]. These SP cells posess higher efficiency and capacity of tumor-sphere formation other than the non-SP group using tumor-sphere culture methods. The presence of efflux pumps in CSCs has been shown to promote drug resistance thereby reducing the efficacy of current therapies. When challenged with chemotherapeutic drugs

in SP cells, this group of cells showed increased resistance to cisplatin, gemcitabine and Vinorelbine compared with the non-SP group [16-18].

Identification of CSC markers

CSCs in solid tumors can be also identified using various CSC markers. Among them, CD133 (also named as prominin-1), is one of those broad-spectrum stemness markers in various kinds of cancer cells including NSCLC which mediates cell differentiation, proliferation and apoptosis [19]. Notably, ASCL1 is an identified regulator of CD133 which induced the expression of CD133 [20]. However, it has been found that the CD133 levels in NSCLC were not significantly related to cancer stemness [21]. Thus there is a critical need to find more selective CSC markers in NSCLC. Besides CD133, ABCG2 has been widely applied to identificate CSCs in lung cancer due to higher tissue specificity than CD133. ABCG2 has been found to play a major role in the multidrug resistance phenotype, and elevated ABCG2 levels have been found in CSC cells in NSCLC. Notably, it has also been found that patients with the dual expression of CD133 and ABCG2 have a relative higher risk of tumor recurrence [22]. In addition, many other CSC markers in lung carcinoma have been also identified in succession. It has been demonstrated that the stem cell-like properties has been enriched in the CD44-expressing subpopulations of H1299 and H23 NSCLC cell lines [23]. CD166 expression also suggests a CSC phenotype in NSCLC [24-25]. Furthermore, an association of CD166+ tumor initiating cells with glycine decarboxylase (GLDC) and the oncogenic stem-cell factor, LIN28B has been established, and GLDChi/CD166+ was found to be a poor prognostic indicator with a shorter overall survival in NSCLC patients [24]. Besides, in Kuang's study, CD90+ tumor spheres from A549 and H446 NSCLC cell lines has a higher self-renewal capacity than CD90– cells [25].

As one member of the Aldehyde dehydrogenases (ALDH) group, ALDH A1 is a putative stem cell marker and is associated with chemical resistance and clinical pathological TNM stages and poor prognosis in NSCLC [26-30]. The developed Aldefluor method could distinguish stem cells from normal cells and has been used to identify potential CSCs in cancer cells including NSCLC [27].

Besides, there are also many other proteins including TMPRSS4, Nestin, Lgr5, coxsackie-adenovirus receptor (CAR), et al. which could be used as CSC markers in NSCLC [29,32-34].

Cancer Stemness Evaluation by Limiting-Dilution Assay

As the golden scale to evaluate the tumor stemness, the *in-vitro* or *in-vivo* limited dilution assay has been widely used to evaluate the efficiency of tumor-sphere formation or tumor generation in nude mice. Briefly, serial dilutions of tumor cells were cultured using serum-free culture methods to compare the rates of tumor sphere formation between different groups. For *in-vivo* analysis of CSCs, different dilutions of cells were injected into nude mice and the rates of tumor formation were calculated and all the data were analysed using Extreme Limiting Dilution Analysis (ELDA). By using this methods, many CSC markers have been identified [35].

Signaling Mediated Cancer Stemness in NSCLC

WNT signaling mediated cancer stemness in NSCLC

The properties of stemness in cancer cells require several molecular cascades including signaling of Notch, Hedgehog and WNT pathways [36]. Among these pathways, aberrant activation of WNT pathway has been found to be the most frequent event associated with higher rates of tumor recurrence and poor prognosis [37]. The carnonical WNT pathway is activated when the ligand WNT3a binds to its cell receptor Frizzled and LRP5/6 complex which can be inhibited by DKK1. Then the destruction of APC complex consisting of APC, GSK3, and AXIN members lead to the failure of degradation of β -catenin by β -Tcrp and the subsequent nuclear entry of β-catenin, and finally lead to the transcription activation of TCF4 targets including CCND1, survivin, c-Myc, *et al.* [38].

It has been reported that the activation of WNT pathway is highly associated with the tumor reccurence and poor patient survival in NSCLC cases. However, the occurrence of the APC mutation event remains poor in NSCLC although this APC mutation event has been widely reported in colon cancer which was positively associated with the CSC-mediated tumor reccurence and chemical resistance. In NSCLC, the epigenetic episodes could be a contributing factor to the activation of WNT pathway according to TCGA data base [39]. Besides, regulation by microRNAs such as mir29, mir582 has been reported to be associated with the aberrant change of WNT signaling in NSCLC, and the activation of WNT pathway by aberrant expression of mir582 was required for their CSC property in NSCLC [40-41].

Notch signaling mediated cancer stemness in NSCLC

Beside WNT pathway, the activation of Notch signaling is another course for the maintence of cancer stemness in solid tumors [42]. The synthesized Notch adaptors form a heterodimer when exported to the cell surface, and bind with the DSLdomains of the receptors of different cells, leading to a subsequent cascade of proteolytic cleavages and the transcription activation of downstream targets [43].

It is worth noting that the level of Notch3 is up regulated in NSCLC patients after chemotherapy which is positively correlated with the level of CD44 and ALDH1A1. Furthermore, the expression of Notch3 is highly associated with poor patient survival and blocking Notch3 inhibited the properties of CSC in NSCLC in an autophagy dependent manner [44].

Hedgehog Signaling Mediated Cancer Stemness in NSCLC

As a classical signal transduction pathway in embryonic development, the hedgehog signaling also play a vital role in tumorgenesis via regulating cell growth and proliferation [45]. The carnonical Hedgehog signaling has two receptors including Patched (Ptc) and Smoothened (Smo), In the presence of Hedgehog, Pct failed to inhibit the activation of Smo, leading to the nucleus entry of the transcription factor Gli and the transcription activation of downstream targets [46].

As demonstrated by many pubulished data, a large group of genes involved in cell proliferarion and cell diffusion including c-Myc, EGF, IGF, PDGF, FGF, Cyclin D, Cyclin E, Cyclin B, BMP have been proved to be the downstream targets of Hedgehog pathway [47]. It has been reported that activation of Hedgehog pathway lead to the elevated expression of snail and ABCG2 and the occurrence of EMT in NSCLC, and the inhibition of the Hedgehog singalling increases cell sensitivities towards cisplatin and erlotinib in NSCLC. A subset of microRNAs responds to the process of Hedgehog inhibition,

including upregulated micro200b and Let-7c with the decreased level of CSC markers including Sox2, Nanog and EpCAM [48]. In addition, there is a crosstalk between Hedgehog signaling and other signaling including AKT, WNT or Notch signaling in dynamic regulation of tumorgenesis [49].

Other molecues involved in cancer stemness in NSCLC

Beside the contribution of WNT, Notch and Hedgehog pathways to cancer stemness in NSCLC, there are also several other molecues which play crucial roles in regulating cancer stemness in NSCLC. As a free radical gaseous molecule, Nitric Oxide (NO) could regulate diverse biological, physiological, and pathological processes among which it can induce the CSC phenotype in NSCLC [50]. As a member of the POU-domain family of transcription factors, Oct4 plays a crucial role in the maintaining the CSC phenotype in CD133-positive cells and confer resistance towards radiation, cisplatin or gefitinib in NSCLC [51-52]. As the main component of the caveolae plasma membranes found in most cell types, caveolin-1 is required for the AKT and ERK signaling activation after chemotherapy using ciprofloxasin and for the maintainence of the CSC phenotype [53]. Rac-1 targeting using small interfering RNA results in the suppression of cancer stemness in NSCLC [54]. In addition, activation of Interleukin-6 signaling is required for the formation of CSCs in NSCLC after therapy [55-56].

Conclusion

Nowadays NSCLC still remains one of the most aggressive malignant tumor diseases which pose threat to people's lives. People with NSCLC especially at higher histologic grades have a relative poorer prognosis due to very high rates of cancer reccurence after therapy. The CSCs theory is currently a very important field in cancer research and well supported in NSCLC since CSCs are associated with tumor metastasis, reccurence and resistance towards therapy. Traditional chemotherapy or other therapies failed to cure patients with NSCLC due to the existence of CSC. Thus, it's necessary to establish CSC identification methods and explore the signaling involved in cancer stemness in NSCLC. In conclusion, This review provides diverse signaling involved in cancer stemess mainly including WNT pathway, Notch pathway and Hedgehog pathway. This review also describes classical identification methods of CSC including side-popoluation, using CSC markers, and carnonical stemness evaluation methods. All of these illustrations will help design new drugs target CSC and promote the development of NSCLC treatment.

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